03.19.03

GP 1642

Please type a plus sign (+) inside this box → [+]

PTO/SB/21 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	08/846,658
Filing Date	May 1, 1997
First Named Inventor	John R. Adair et al.
Group Art Unit	1642
Examiner Name	Minh Tam B. Davis
Total Number of Papers in This Submission: One	Attorney Docket Number: CARP0001-100

ENCLOSURES *(check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☒ Supplemental Amendment
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
  - ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Continued Examination (RCE)
- ☐ CD, Number of CD(s)
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) *(please identify below)*: **Exhibits 1 – 9**

Remarks

EXPRESS MAIL LABEL NO.: EV147 612 604US
DATE OF DEPOSIT: March 17, 2003

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm *or* Individual name	Doreen Yatko Trujillo, Reg. No. 35,719 Cozen O'Connor, P.C.
Signature	Doreen Yatko Trujillo
Date	March 17, 2003

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail Service in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on this date: March 17, 2003

Typed or printed name	Doreen Yatko Trujillo, Reg. No. 35,719		
Signature	Doreen Yatko Trujillo	Date	March 17, 2003

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be send to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

DOCKET NO. CARP0001-100 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#46

In Re Application of: Adair et al.
Serial No.: 08/846,658
Filing Date: May 1, 1997
For: HUMANISED ANTIBODIES

Confirmation No. 9631
Group Art Unit: 1642
Examiner: Minh Tam B. Davis

EXPRESS MAIL NO.: EV147 612 604US
Date of Deposit: March 17, 2003

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

SUPPLEMENTAL AMENDMENT

This paper is being filed following the helpful personal interview conducted on January 21, 2003. A Request for Continued Examination, with an accompanying Request for Reconsideration, was filed December 23, 2002 in response to the Final Rejection dated December 18, 2001, following a Notice of Appeal filed June 18, 2002, received by the Patent Office June 24, 2002. This amendment is supplementary to that request and presents arguments made during the interview.

Claims 24-31 were pending. All pending claims were rejected in the Final Rejection. A Request for Reconsideration was submitted May 20, 2002. An Advisory Action was mailed August 28, 2002. The Advisory Action indicated that the rejection of the claims under 35 U.S.C. §102(e) over U.S. Patent No. 5,585,089 (the Queen patent) was maintained. Applicants respectfully request withdrawal of this rejection in view of the documents submitted May 20, 2002, the Request for Reconsideration submitted December 23, 2002, and the following arguments.

In maintaining this rejection, it has been the Examiner's position that the Queen patent is entitled to the filing dates of its two earliest priority applications when used as a reference under 35 U.S.C. §102(e). Specifically, contrary to Applicants' position, the Examiner maintains that the priority applications in question provide written descriptive support for the phrase "outside

the Kabat and Chothia CDRs" in the claims as issued. The Examiner's basis for this position is essentially a single sentence in the earliest filed application as follows:

> The chains all exhibit the same general structure of relatively conserved framework regions joined by three hypervariable regions, also called CDR's (see, "Sequences of Proteins of Immunological Interest," Kabat, E., et al., U.S. Department of Health and Human Services, (1983); and Cholthia [sic] and Lesk, J. Mol. Biol., 196:901-917 (1987), which are incorporated herein by reference.)

(Application Serial No. 07/290,975, "the '975 application," paragraph bridging pages 9-10.) The Examiner argues that this sentence supports her interpretation that any reference to CDR in the claims of the Queen patent means the Kabat plus Chothia CDRs. Applicants maintain that this interpretation is inconsistent with Chothia and Lesk, the remainder of the '975 specification, the prosecution history, and, finally, the claims themselves.

First, although the quoted sentence cites the Chothia and Lesk reference, and incorporates it by reference, Chothia and Lesk does not support the Examiner's interpretation that CDR means Kabat plus Chothia. Chothia and Lesk carefully distinguishes its "hypervariable loops" from Kabat's CDRs.

> The six loops, whose main-chain conformations vary and which are part of the antibody combining site, are formed by residues 26 to 32, 50 to 52 and 91 to 96 in VL domains, and 26 to 32, 53 to 55 and 96 to 101 in the VH domains L1, L2, L3, H1, H2, and H3, respectively. **Their limits are somewhat different from those of the complementarity-determining regions defined by Kabat et al.** (1983) on the basis of sequence variability: residues 24 to 34, 50 to 56, and 89 to 97 in VL and 31 to 35, 50 to 65 and 95 to 102 in VH.

(Chothia and Lesk, "Canonical Structures for the Hypervariable Regions of Immunoglobulins," *J. Mol. Biol.*, vol. 196, p. 904, 1987, emphasis added.)

Second, the remainder of the specification of the '975 application indicates that references to CDRs are as defined as Kabat. For example, on page 10, line 2, the framework regions are defined in terms of Kabat (copy enclosed, Exhibit 1). If the framework regions are defined in terms of Kabat, the CDRs must be as well. On page 21 (copy enclosed, Exhibit 2), the protocol for selecting which residues in the heavy chain are to be donor is set out. At lines 19-22, residues which fall in positions within a CDR **"as defined by Kabat, [i.e.,] amino acids 31-35, 50-66, and 99-106"** are specified to be donor.[1] At lines 28-30, amino acid 30 is listed as a position **immediately adjacent to a CDR** to be changed to donor. Amino acid 30 is adjacent the first heavy chain Kabat CDR, but **within** the first heavy chain Chothia hypervariable loop. The description of Figure 1 of the '975 application indicates that it refers to the heavy chains and that the three CDRs are underlined (page 6, lines 1-6, copy enclosed, Exhibit 3). In Figure 1 (copy enclosed, Exhibit 4), only amino acids **31-35** are underlined for CDR1.

Third, Queen never so argued. In fact, rather than argue that CDR means Kabat plus Chothia, Queen added what ultimately became the recitation "outside the Kabat and Chothia CDRs" to overcome an obviousness rejection over, *inter alia*, the Riechmann reference. (See Paper No. 7, Application Serial No. 07/634,278, filed December 19, 1990, Exhibit 5, page 7.) The Riechmann reference discloses an antibody in which the CDRs (as defined by Kabat) and, additionally, residue 27 alone or residues 27 and 30 are changed to donor. The claims under rejection at the time recited that the CDRs "and **at least one** residue immediately adjacent to at least one of said CDRs are from different immunoglobulin molecules than the framework regions." (Paper No. 6, Application Serial No. 07/634,278, filed December 19, 1990, Exhibit 6, page 1, emphasis added.) As noted above, the Kabat CDR1 for the heavy chain comprises residues 31-35. Residue 30 is, thus, immediately adjacent to at least one of the Kabat CDRs.

In response, the claims were amended to recite that the framework changes were "not in positions 26-30 of the heavy chain." (See Paper No. 10, Application Serial No. 07/634,278, filed

[1] The '975 application uses a linear numbering system. Accordingly, the CDR residues listed differ slightly from those listed in the foregoing passage cited from Chothia and Lesk, in which the Kabat numbering system was used.

December 19, 1990, Exhibit 7, page 3.)[2] Queen argued that the "[t]he position 27 and 30 modifications of Reichmann [sic] et al. were in fact within the Chothia-Lesk H1 CDR, rather than outside this CDR." *Id.*, at page 17. Notably, Queen did not argue that the modifications were in the CDRs as those terms were used in the claims. The examiner, however, objected to the negative limitation language, because the example antibodies in the then specification showed changes at residues 27 and 30. The claims were then amended to recite framework changes "in addition to any such donor amino acids in positions 26-30 of the heavy chain." (See Paper No. 17, Application Serial No. 07/634,278, filed December 19, 1990, Exhibit 8, page 2.) Again, Queen did not argue that residues 26-30 were already part of the CDRs as those terms were used in the claims. The rejection of the claims for obviousness over, *inter alia*, Riechmann was maintained. A continuation application was then filed. The claims were amended in a concurrently filed Preliminary Amendment to recite "outside the Kabat and Chothia CDRs." (Paper No. 3, Application Serial No. 08/477,728, filed June 7, 1995, page 1.) The claims were allowed shortly thereafter.

Additionally, during prosecution of the parent of the application that issued as the Queen patent, a Glossary was submitted with an Appeal Brief which stated the following regarding the definition of Complementarity Determining Regions:

> Two related but **distinct** definitions of the CDRs are in use – the **original** definition of **Kabat** (based on sequence variability), and the **newer** definition of **Chothia** (based on 3-D structure).

(Paper No. 24, Application Serial No. 07/634,278, filed December 19, 1990, page 1 of the Glossary, copy attached, Exhibit 9, emphasis added in part.)[3] There is no mention of a "combined" definition.

[2] A Kabat plus Chothia CDR for CDR1 of the heavy chain would comprise residues 26-35 and, thus, would include residues 26-30.

[3] To the best of the undersigned's knowledge based upon a review of the prosecution history of the Queen patent, Queen did not argue that CDR meant Kabat plus Chothia in response to the rejection over Riechmann. Instead, Queen added the limitation that the changes were to be"outside the Kabat and Chothia CDRs."

Finally, if CDR means Kabat plus Chothia as the Examiner maintains, the recitation in the claims "outside the Kabat and Chothia" preceding CDRs is superfluous. For example, see claim 1 of the Queen patent duplicated below.

> 1. A humanized immunoglobulin having **complementarity determining regions (CDRs)** from a donor immunoglobulin and heavy and light chain variable region frameworks from human acceptor immunoglobulin heavy and light chains, which humanized immunoglobulin specifically binds to an antigen with an affinity constant of at least 10^7 M^{-1} and no greater than about four-fold that of the donor immunoglobulin, wherein said humanized immunoglobulin comprises amino acids from the donor immunoglobulin framework outside the **Kabat and Chothia CDRs**, wherein the donor amino acids replace corresponding amino acids in the acceptor immunoglobulin heavy or light chain frameworks, and each of said donor amino acids:
>
> (I) is adjacent to **a CDR** in the donor immunoglobulin sequence or
>
> (II) contains an atom within a distance of 4Å of **a CDR** in said humanized immunoglobulin.

(Claim 1, U.S. No. 5,585,089, emphasis added.) As is evident from the claim, three other passages within the claim refer merely to CDRs without further qualification. If CDR means Kabat plus Chothia as advanced by the Examiner, there would be no need to recite "outside the Kabat and Chothia CDRs" after the first reference to CDR because any framework changes to donor would be, by definition, outside the Kabat and Chothia CDRs.

Applicants maintain that there is no written descriptive support in the two earliest filed applications for the requirement that the changes to donor be outside the Kabat **and** Chothia CDRs as recited in the claims as issued in the Queen patent. In further support thereof, the Examiner is directed to the patentees' own admissions regarding the same as set forth in Applicants' responses filed May 20, 2002 and December 23, 2002, discussion incorporated herein.

Applicants respectfully submit that the application is in condition for allowance and request declaration of an interference. If the Examiner disagrees, or feels a telephonic interview would be helpful, she is asked to contact the undersigned at 215-665-5593 to discuss.

Respectfully submitted,

Date: 3/17/2003

Doreen Yatko Trujillo
Registration No. 35,719

COZEN O CONNOR P.C.
1900 Market Street, 6th Floor
Philadelphia, PA 19103-3508
(215) 665-5593 - Telephone
(215) 701-2005 - Facsimile